UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/605,708	10/21/2003	Zhiyuan Gong	GLOF:007USC1	2707

32425 7590 07/09/2007
FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
07/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/605,708	GONG ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-28 and 30-42* is/are pending in the application.

4a) Of the above claim(s) *17,18,22,23,25-28,33 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-16,19-21,24 and 30-32, 35-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/913,898.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on May 5, 2007, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below: Pete Paras

Applicant's amendment filed on February 5, 2007, has been received and entered. Claims 1, 15 –16, 24, 30, 32, 36 and 39 have been amended, while claims 4-8 and 29 is canceled.

Election/Restrictions

Applicant's election of claims 1-16, 20-21, 29-32 and 35-41 in the reply filed on January 19, 2006 was acknowledged. The applicants elected muscle specific promoter examination. It is noted claim 19 is directed to muscle specific promoter and therefore claim 19 is rejoined with elected groups. It is noted that applicants have also amended previously withdrawn claim 24, which is also rejoined for the examination purposes to the extent it reads on elected invention. Claims 17-18, 22-23, 25-28 and 33-34 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a

nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction/election requirement in the reply filed on 1/19/2006.

Claims 1-3, 9-16, 19-21, 24, 30-32, 35-42 are currently under examination.

Withdrawn--Claim Rejections - 35 USC § 112

Claims 1-16, 20-21, 29-32 and 35-42 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn. Upon further consideration examiner would agree with applicants' assertion that specification supports the description of a transgenic fish that expresses one or more fluorescent protein.

New Grounds of Claim Rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-16, 24, 30-32, 35-41 and 42 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method of providing transgenic fish to the ornamental fish market comprising the step of (a) obtaining a transgenic ornamental fish comprising a chimeric gene comprising a promoter that drives the expression of a fluorescent protein selected from a group consisting of BFP, YFP and CFP predominantly in muscles of said fish, said promoter being a muscle specific promoter, such that said transgenic fish expresses fluorescent protein encoded by fluorescent gene in skeletal muscle at a level sufficient such that said transgenic fish fluoresces upon exposure to one or more light and (b) distributing said fish to the

ornamental fish market, does not reasonably provide enablement for using any promoter other then muscle specific promoter to obtain transgenic fish suitable for ornamental fish market. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 1-3, 9-16, 24, 30-32, 35-42 are broad in scope. The following paragraph will outline the full scope of the claims. Claimed invention recites a method of providing transgenic fish to the ornamental fish market by obtaining transgenic fish comprising one or more chimeric fluorescent genes operably linked to a promoter such that transgenic fish expresses one or more fluorescent gene. Claims are also directed to to obtain transgenic fish comprising fluorescent gene under control of any promoter such that it expresses more than one color of fluorescent protein. Claim 30 limits the expression of color in same tissue to affect an original color. Claim 31 limits the

fluorescent gene of claim 30 to include GFP and BFP. Claim 32 limits the method of claim 29 to include more than one fluorescent protein that are separately expressed in different tissues. Claims 36-41 limit the method of claim 1 to include stable transgenic fish line.

These claims embrace obtaining transgenic fish comprising fluorescent gene under control of promoter such that fish express protein at any level and distributing said fish to the ornamental fish market. The breadth of the promoter includes promoter of any species and any length. Prior to instant invention, Betancourt et al (Mol Mar Biol Biotechnol. 1993, 2(3): 181-8,. art of record) described, "elements from mammalian genes may not be properly recognized by the fish cellular machinery and in an unpredictable manner" (see abstract). Previously, Stuart et al (Development. 1990; 109(3):577-84) examined the reproducibility of tissue-specific expression of the foreign genes, each of which contained both a Rous sarcoma virus long terminal repeat (RSV-LTR) and an SV-40 early promoter. The results indicated that in spite of this construct reproducibly expressed in a similar subset of tissues; an analysis of gene expression at the cellular level reveals a variegated pattern of transgene expression (see page 578, col. 1, para. 1 and Table 2). The CAT-specific antibody revealed CAT expression in epithelial cells of hemizygous CATfish progeny and the level of expression in individual cells varied greatly. In fact the expression was undetectable in a relatively large fraction of these cells (Fig. 4). It is noted that Stuart contemplated this uneven expression pattern could result either somatic mutation (e.g. transgene instability) or mosaic gene activation or inactivation (see 583, col.1, last para.). This is further supported by the instant specification that indicated that use of heterologous gene promoter from SV 40 and RSV and other promoters in studying zebrafish showed variable and unpredictable expression pattern (see pages 5, 6 and 15 of the specification, paragraph 6 and also paragraph 28). In light of the above discussion, the issues of unpredictability, with respect to use of promoter in obtaining transgenic ornamental fish, relate more towards choice of promoter that could greatly effect the levels of fluorescent expression visible in normal sunlight or under blue light. It is apparent from the preceding discussion that disclosure provided by the applicant, in view of prior art, must encompass a wide area

of knowledge to a reasonably comprehensive extent. In other word each of those, aspect considered broad must be shown to a reasonable extent so that one of the ordinary skills in the art at the time of invention by applicant would be able to make and use the invention without any undue burden being on such Artisan.

The specification broadly discloses role of transgenic fish in medical research and method of introducing foreign gene in fish (pp. 3). The invention is based in part to develop fluorescent transgenic ornamental fish using fluorescent gene constructs. The specification generally describes use of different gene promoters that could express plurality of fluorescent gene in different tissue (pp 7). Pages 9-15 provide brief description of drawing. Pages 15-47 provide detailed description of the invention, preferred embodiment, gene construct and general method to prepare fluorescent transgenic fish and other techniques disclosed in the instant application. Remaining specification describes the specific example of the ornamental transgenic carrying characteristics similar to one described in this office action. Example 1: of specification teaches isolation of muscle specific and ubiquitously expressed zebrafish cDNA clones. Example 2 discloses isolation of four-zebrafish gene promoters. Example 3 describes generation of green fluorescent transgenic fish. The specification describes several construct comprising MLC2f promoter, however, only two-construct containing promoter fragment (2011 bp and 1338 bp) are capable of maintaining the high level of expression. The highest expression was seen with only 2 -Kb promoter suggesting the importance of promoter region of 1338 bp to 2011 bp for conferring the highest promoter activity. While the specification has contemplated that methods of the invention may be used to create transgenic fish of any species using any promoter, the guidance provided by the specification correlated only to muscle specific promoters.

It is noted that specification exemplified GFP transgenic fish emits green fluorescence light under a blue or ultraviolet light and this feature makes the genetically engineered fish unique and attractive in the ornamental fish market (see paragraph 13 of the published application). Based on the applicant's disclosure it appears that the intended purpose of obtaining transgenic fish is to provide fluorescent fish to ornamental fish market for display purposes. Furthermore it is generally known in the art and

described by applicants that ornamental and aquarium fish are defined as fish that are produced and maintained solely for exhibit purpose (see applicants' argument and FDA fish classification Guide, filed 8/11/2006, page 13). It is noted that prior art teaches numerous factors that potentially affect the transgenic frequency or expression levels in transgenic fish including (i) expression levels that do not strongly correlated to transgenic frequency; and (ii) placement of construct (Higashijima et al (Dev Biol. 1997; 192(2): 289-99; art of record). The intent is not to say that transgenic fish comprising fluorescent gene cannot be made rather art of making transgenic ornamental fish for the distribution in ornamental fish market is unpredictable and dependent on a strong promoter that works well in different species of fish and capable of showing high level of fluorescent gene expression. The specification has exemplified a method describing generation of transgenic founder zebrafish containing pMLC2f-EGFP that emits a strong green fluorescent light under a blue or ultraviolet light (see Figure 11A). It is noted that specification describes the importance of fragments of MLC2f promoter (2011 bp and 1338 bp) that are capable of maintaining the high level of expression. The highest expression was seen with only 2 -Kb promoter suggesting the importance of the promoter region of 1338 bp to 2011 bp for conferring the highest promoter activity (see page 42, para 89 of the specification). Thus specification has provided a working example correlating only to specific region of muscle specific MLC2f promoter that conferred the expression that could be observed when the fish is exposed to sunlight. Prior to instant invention, transgenic fish that are capable of expressing heterologous gene were generally known in prior art (See Copper et al, US patent 5,998698, IDS; Kuo et al, 1995, Kim et al, 1996, Hackett et al 1993; all of the record and cited by applicant in appeal brief). However, it is emphasized that in all instances, the transgenic fish displayed expression of transgene or fluorescent protein that was visible only under microscope. Moreover none of previously developed transgenic lines displayed expression or fluorescent color visible to unaided eyes. In fact, applicant's own post filing art, describes the problem in generating transgenic fish suitable for ornamental fish market. Specifically Gong et al (Biochem Biophys Res Commun. 2003; 308(1): 58-63) state "the mylz2 promoter is likely the strongest muscle-specific promoter'. Gong further

describes "availability of several GFP transgenic zebrafish that have been produced using many different tissue-specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes. Thus, one key to success in the generation of colorful transgenic ornamental fish is in the strength of the promoter. Another factor is the selection of tissue; the muscle constitutes majority of the body and thus synthesizes more and visible color proteins. In contrast, transgenic GFP expression in only a single layer of skin cells cannot be visualized without using a fluorescent microscope (page 62, col. 2, para. 1)." It is clear from the teaching of Gong et al that strong expression of fluorescent gene under the control of MLC2 promoter in muscle tissue that constitutes majority of the fish body tissue is vital for successfully generating transgenic fish for distribution in ornamental fish market.

In the instant case, claims are drawn to obtain a transgenic fish comprising fluorescent gene under control of any promoter such that it expresses fluorescent protein and distributing such fish in ornamental fish market. It is apparent from the teaching of Gong et al that generation of transgenic fish which is suitable for distribution in ornamental fish market requires strong muscle specific promoter or other strong tissue specific promoter that may require exposure of fish to a light of specific wavelength selected to be optimal for the fluorescent protein in order to visualize fluorescence on the fish. Examiner has indicated variable and unpredictable expression pattern which is also supported by post filing art indicating many tissue specific promoter that are capable of expressing heterologous gene in fish are not suitable for use in generating transgenic ornamental fish (see Gong et al and references therein). In view of foregoing discussion it is apparent that specification has failed to provide relevant teachings or specific guidance correlating to transgenic fish comprising fluorescent gene under control of any promoter other then exemplified muscle specific promoters that are suitable for generating transgenic ornamental fish intended for distribution in ornamental fish market. In fact, the prior art , specification and post filing art reports that not all promoters function well in fish and a very stromg muscle specific promoter is required to show high level of expression in muscle tissue that constitutes

majority of the fish body tissue is key to success in generating transgenic fish for ornamental fish market (supra).

It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success. It is apparent that choice of a promoter could greatly effect the level of expression in transgenic ornamental fish. Given such differences in the expression of a fluorescent gene as embraced by the claims, particularly when taken with the lack of guidance provided by the specification, it would require undue experimenattaion to emperically test different tissue specific promoter or promoter regions, level of the fluorescent gene expresion, the conseqeunce of that expresion and therefore its suitability for distribution in ornamnetal fish market. The cited art of Gong et al and references therein clearly shows that obtaining transgenic fish comprising fluorescent gene required strong muscle specific promoters for displaying fluorescence in order for it to be suitable for distribution in ornamental fish market.

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966),* Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In the instant case, the specification has failed to report obtaining a transgenic fish comprising fluorescent gene under control of any promoter other then one exemplified that is suitable for distribution to ornamental fish market.

In conclusion, in view of breadth of the claims and absence of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions commensurate with full scope of the claim. The specification and prior art do not teach method of obtaining

transgenic fish comprising fluorescent gene under control of any promoter and distributing said fish to ornamental fish market commensurate with full scope of the claims. An artisan of skill would have to perform undue experimentation to make and use the invention because the art of making transgenic fish using any promoter for distribution of said fish in ornamental fish was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant's arguments and appeal brief filed May 7, with respect to fish species claimed is persuasive and therefore rejection pertaining to this issue is withdrawn. However, applicant's argument for obtaining transgenic fish comprising one or more fluorescent gene under control of any promoter wherein transgenic fish expresses one or more fluorescent protein intended for distribution of such fish in ornamental fish market have been fully considered but they are not fully persuasive. Applicants in their argument on pages 6-8 cite a number of publications to suggest that obtaining transgenic fish was routine (see Cooper US Patent 5, 998, 698, Kuo et al, Kim et al, Moss et al, Hackett et al). Applicants also assert that Examiner has cited references that are old and support enablement. Applicant also argues that contrary to Examiner's argument there is no requirement that the fish express at any level particular level. Applicants further asserts that if transgenic fish do not express the fluorescence at a high desirable level they may not be very desirable to the ornamental fish market and not be well received commercially, but there is no enablement issue.

In response, as an initial matter it is noted that Examiner has broaden the scope of claimed invention to recite (a) obtaining transgenic ornamental fish that drives the expression of a fluorescent protein selected from a group consisting of BFP, YFP and CFP predominantly in muscles of said fish, said promoter being a muscle specific promoter, such that said transgenic fish expresses fluorescent protein encoded by fluorescent gene in skeletal muscle; at a level sufficient such that said transgenic fish fluoresces upon exposure to one or more light and (b) distributing said fish to the

ornamental fish market. Therefore, applicant arguments with respect use of muscle specific promoter are moot.

In response to applicant's argument that method of making transgenic fish using any promoter is enabled and there is no requirement of any specific level of expression. It is emphasized that independent claims 1 and 15 are directed to a method of providing a transgenic ornamental fish by obtaining a fish that expresses fluorescent gene under control of any promoter and distributing the fish to ornamental fish market. It is noted that claims 1, 9-16, 24, 30-32, 35-42 require distribution of transgenic fish to ornamental fish market by obtaining transgenic fish that express fluorescence. There is no requirement that these fish show fluorescence under light of any specific wavelength. In other words, claims 1, 9-16, 24, 30-32, 35-42 embrace transgenic fish that shows fluorescence, which could be visualized under normal sun light. However, the examiner asserts that all the art cited by applicants in support of enablement (Cooper US Patent 5, 998, 698, Kuo et al, Kim et al, Moss et al, Hackett et) displayed expression of transgene or fluorescent protein only under microscope and in fact none of previously developed transgenic lines displayed expression or fluorescent color visible to unaided eyes. It is generally known in the art as well as previously defined by the applicants that ornamental and aquarium fish are defined as fish that are produced and maintained solely for exhibit purpose (see applicants' argument and FDA fish classification Guide, filed 8/11/2006, page 13). Therefore, in spite of no requirements in claims for any specific level of fluorescence in transgenic fish, it is reasonable to expect that transgenic fish intended for distribution in ornamental fish market requires higher expression level of fluorescent gene in order for fish to be suitable for its intended purpose. The specification described that use of heterologous gene promoter from SV 40 and RSV and other promoters in studying zebrafish showed variable and unpredictable expression pattern of a transgene (see page 6, 7 and 15 of the specification, paragraph 6 and also paragraph 28; emphasis added). Examiner has cited refernces to indicate variable expression pattern with different promoters. In addition, Examiner has now included post-filing art of the applicants describing the problem in generating transgenic fish suitable for ornamental fish market using any promoter other then muscle or skin

specific strong promoter. It is noted that contrary to applicants main assertion of using any promoter in obtaining transgenic fish, applicants himself states that "availability of several GFP transgenic zebrafish that have been produced using many different tissue-specific promoters (also see references therein), but none of these transgenic lines display fluorescent color visible to unaided eyes. Thus, one key to success in the generation of colorful transgenic ornamental fish is in the strength of the promoter. Another factor is the selection of tissue; the muscle constitutes majority of the body and thus synthesizes more and visible color proteins. In contrast, transgenic GFP expression in only a single layer of skin cells cannot be visualized without using a fluorescent microscope (Gong et al, supra, page 62, col. 2, para. 1)". It is noted that applicants have described in spite of availability of several transgenic line that uses tissue specific promoters, none of these transgenic fish made by using tissue specific promoter were suitable for ornamental fish market. Gong et al clearly suggest importance of strength of the promoter and selection of tissue specificity in obtaining transgenic fish suitable for ornamental fish market. It is apparent that choice of a promoter could greatly effect the level of expression in transgenic ornamental fish. Given such differences in the expression of a fluorescent gene as embraced by the claims, particularly when taken with the lack of guidancein the specification, an artisan would have to make new invention to determine tissue specific promoter or promoter regions, level of the fluorescent gene expresion, the conseqeunce of that expresion and its suitability for distribution in ornamnetal fish market.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1-8, 16 and 36-42 rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS) and Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998) is withdrawn in view of amendments to the independent claims. It is noted that applicants have canceled GFP from independent claim to overcome the art.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-16, 19, 24, 30-32, 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York, 1998) and Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record).

Higashijima et al teach a method of generating transgenic zebrafish comprising fluorescent gene under the control of beta actin promoter. Specifically, Higashijima et al disclose using a β-actin–GFP construct. Higashijima et al show GFP is expressed throughout the body of one line whereas other two transgenic lines showed identical spatial expression of GFP in muscle cells (pp 295, col. 1, para 2, Fig 4), demonstrating consistent expression of green fluorescence. It is also noted that Higashijima et al show stable transmission of GFP expression in three lines of F3 generation suggesting that transgene is stably integrated into the genome of each line (pp 297, col. 1, para 1). It is also disclosed that fluorescence expression could be seen with FITC filter suggesting that fluorescent expression on fish could be best viewed at excitation wavelength of blue light (360-420 nm) (pp 292, col.2, para 2). However, Higashijima et al do not teach obtaining transgenic fish comprising other fluorescent gene and distribution of said transgenic fish to the ornamental fish market.

However, at the time the claimed invention was made, other fluorescent genes were available in prior art. Chalfie disclosed cloning of cDNA for green fluorescent protein (GFP) originally isolated from the jellyfish that is modified by site-directed mutagenesis for different emission spectra and thus several artificial fluorescent color

proteins including yellow fluorescent protein (YFP), blue fluorescent protein (BFP), and cyan fluorescent protein (CFP) were available prior to instant invention (see pages 29-30, 244-246, especially pages 30 and 245, para 1 and 2). Chalfie differed from the claimed invention by not teaching expressing fluorescent gene in transgenic fish.

Bryan et at teach a combinations containing a first composition containing a luciferase and a second composition containing one or more additional components of a bioluminescence-generating system for use to produce novelty items. These novelty items also include transgenic fish, particularly transgenic fish that express a luciferase (col. 8, line 16). It is noted that these novelty items are designed for entertainment, recreation and amusement including use of the item to attract attention (col. 8, lines 25-29). Bryan et al also disclose that such uses of the novelty item may in the place of normal or ordinary uses of such an item (col. 8, line 33). Thus, teachings of Bryan et al encompass color displaying fish in ornamental fish market. However, Bryan et al do not specifically teach obtaining ornamental transgenic fish comprising a promoter operably linked to a fluorescent gene.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Higashijima by providing fluorescent transgenic fish as novelty item to ornamental fish market as described by Bryan. Higashijima et al had already disclosed a method for making fluorescence transgenic fish displaying fluorescence in the muscle of the fish. In addition, Bryan et al had described that novelty items such as transgenic fish comprising fluorescent genes could be designed for entertainment, recreation and amusement including use of the item to attract attention (col. 8, lines 25-29). One of ordinary skill in the art would have been motivated to modify the method of Higashijima to replace GFP with other fluorescent gene such as BFP, YFP, CFP as disclosed by Chalife. This would have allowed person of ordinary skill to express different fluorescent color for distribution of transgenic fish displaying different color as novelty item for display at public place as suggested by Bryan.

One who would have practiced the invention would have had reasonable expectation of successfully obtaining a transgenic fish comprising fluorescent gene and distributing in the market because Higashijima already taught a method for making

fluorescent transgenic fish and Bryan had taught fluorescent transgenic fish could be made for entertainment, recreation and amusement including use of the item to attract attention. One of ordinary skill in art would have been motivated to combine the teaching Higashijima, Chalfie and Bryan because a fluorescent transgenic fish comprising one or more fluorescent gene operably linked to a promoter would have provided fluorescent fish that would have attracted attention upon distribution of color displaying transgenic fish as a novelty item in a place of normal or ordinary uses of such an item (pet store or ornamental fish market) as taught by Bryan.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York, 1998), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record) as applied to claims 1, 9-16, 19, 24, 30-32, 35-42 above, and further in view of Abeywickrama et al (US Patent no: 5, 028,839, dated 7/2/1991).

The combined teachings of Higashijima et al, Chalfie, et al, Bryan have been discussed above and relied in same manner here. Although, Higashijima implicitly taught viewing the transgenic fish under the fluorescent microscope but cited references differed from claimed as none of the references explicitly teach displaying fish under blue or any other light source.

Prior to instant invention, use of fluorescent lamp in aquaria was well known to person of ordinary skill. Specifically, Abeywickrama et al teach fluorescent lamp including a luminescent layer comprising a mixture of red, green and blue phosphors, each phosphor when the lamp is in use emitting light in a respective spectral region, the red phosphor emitting predominantly in the spectral region of from 610 nm to 620 nm, the green phosphor emitting predominantly in the spectral region of from 540 nm to 545 nm and the blue phosphor having a peak emission wavelength in the spectral region

from 430 nm to 480 nm (see abstract and claim 3). However, Abeywickrama et al did not disclose displaying transgenic fluorescent fish under lamp emitting light in different spectra region.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Higashijima, Chalfie and Bryan by displaying the transgenic fluorescent fish under lamp emitting light in different spectra region in order to better visualize the fluorescence emitting fish. Higashijima and Chalfie provided motivation by indicating that different fluorescence gene have different emission spectra and Higashijima specifically viewed transgenic fish expressing GFP under fluorescent lamp (488nm). One who would have practiced the invention would have had reasonable expectation of successfully displaying the transgenic fish comprising fluorescent gene under light emitting different wavelength as disclosed by Abeywickrama for displaying fluorescent transgenic fish for entertainment, recreation and amusement as taught by Bryan. One of ordinary skill in art would have been motivated to combine the teaching Higashijima, Chalfie, Bryan and Abeywickrama because a fluorescent transgenic fish comprising one or more fluorescent gene operably linked to a promoter displayed under lamp emitting light of different emission spectra would have provided fluorescent fish that would have attracted attention upon distribution of fluorescent transgenic fish as a novelty item in a pet store or ornamental fish market as taught by Bryan.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York, 1998), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record) as applied to claims 1, 9-16, 19, 24, 30-32, 35-42 above, and further

in view of Moss et al (Gene. 1996; 173: 89-98, IDS) or Chan et al (Abstract of paper presented at 1994 meeting on Zebrafish development and Genetics, abstract, IDS.

The combined teachings of Higashijima et al, Chalfie, et al, Bryan et al have been discussed above and relied in same manner here. Although, Higashijima taught a transgenic fish comprising fluorescent gene under control of muscle specific promoter but Higashijima differed from claimed invention by not explicitly teaching use of other muscle specific promoter such as MLC2 gene promoter.

Prior to instant invention, Moss et al. teach a zebrafish that comprises a myosin light chain enhancer operatively linked to a sequence encoding GFP for the muscle specific expression. Characterization of the resulting fish indicated fluorescence from expression of the transgene was seen uniquely in the muscle and not other non-muscle cells in the fish. In addition, Chan et al disclosed fast skeletal isoforms of the regulatory MLC2 gene and also disclose successful cloning of amplified promoter of 1 KB promoter fragment showing several muscle specific fragment and two putative TATA boxes. However, neither Moss nor Chan taught distributing transgenic fluorescent fish to ornamental fish market.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Higashijima to replace beta-actin promoter with other muscle specific promoter such as MLC as disclosed by Chan or Moss particularly since 1.0Kb fragment of MLC2 gene showed muscle specific elements and several TATA boxes while Moss showed the specificity of expression in muscles of Zebrafish. One who would have practiced the invention would have had reasonable expectation of successfully modifying the construct disclosed by Higashijima to replace beta actin promoter with MLC2 promoter as both Moss and Chan taught specificity of expression in muscle cells in the fish. One of ordinary skill in art would have been motivated to combine the teaching Higashijima, Moss or Chan, Chalfie and Bryan because a fluorescent transgenic fish comprising one or more fluorescent gene operably linked to a muscle specific promoter such as MLC2 would have provided strong muscles specific fluorescence that would attract attention upon distribution of fluorescent transgenic fish

as a novelty item in a place of normal or ordinary uses of such an item (pet store or ornamental fish market) as taught by Bryan.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Chalfie, et al Green fluorescent protein: properties, applications, and protocols, Wiley-Liss, New York, 1998), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record) as applied to claims 1, 9-16, 19, 24, 30-32, 35-42 above, and further in view of Liao et al (Analytical Biochemistry, 253, 1997, 137-139, IDS).

The combined teachings of Higashijima et al, Chalfie, et al, Bryan et al have been discussed above and relied in same manner here. Although, Higashijima taught a transgenic fish comprising fluorescent gene under control of muscle specific promoter but differed from claimed invention by not teaching the use of MCK promoter.

Prior to instant invention, Liao teaches successful isolation of a 4.3 kb promoter region from a zebrafish cytokeratin gene. However, Liao et al did not teach distributing transgenic fluorescent fish to ornamental fish market.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Higashijima to replace beta-actin promoter with other muscle specific promoter such as MCK as disclosed by Liao. One who would have practiced the invention would have had reasonable expectation of successfully modifying the construct disclosed by Higashijima to replace beta actin promoter with MCK promoter since Higashijima had already indicated that tissue specific promoter/enhancer from zebrafish origin work well in zebrafish (see page 290, col. 1, last para. bridging to col. 2, page 298, col. 2, para. 1). One of ordinary skill in art would have been motivated to combine the teaching Higashijima, Liao, Chalfie and Bryan because a fluorescent transgenic fish comprising one or more fluorescent gene operably linked to a muscle specific promoter such as MCK would have provided strong

muscles specific fluorescence that would have attracted attention upon distribution of fluorescent transgenic fish as a novelty item in a place of normal or ordinary uses of such an item (pet store or ornamental fish market) as taught by Bryan.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1, 9-16, 19, 24, 30-32, 35-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Higashijima et al (Dev Biol. 1997; 192(2): 289-99, IDS), Bryan et at (US Patent no. 6436682 8/20/2002, filing date, 6/30/ 2000, effective filing date 3/ 27/ 1998, art of record), Yang et al (1998; 273(14):8212-6, IDS) and Living Colors Subcellular Localization Vectors (October 1998) CLONTECHniques XIII (4):8-9.

The combined teachings of Higashijima et al, and Bryan et al have been discussed above and relied in same manner here.

At the time the claimed invention was made, GFP and other variants of GFP were available in prior art. CLONTECHniques disclosed availability of enhanced cyan fluorescent protein (ECFP), an alternative to enhanced blue fluorescent protein and enhanced yellow fluorescent protein (EYFP) color variants (see page 8 and 9), while Yang et al taught to combine a blue emission mutant of GFP containing four point mutations (Phe-64 to Leu, Ser-65 to Thr, Tyr-66 to His, and Tyr-145 to Phe) with a synthetic gene sequence containing codons preferentially found in highly expressed human proteins to overcome the dim fluorescence and low expression levels attained in higher eukaryotes with such variants (see abstract). However, Yang and Clontechnique different from claimed invention by not teaching transgenic fish comprising fluorescent protein under control of promoter.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Higashijima by providing fluorescent transgenic fish as novelty item to ornamental fish market as described by Bryan. Higashijima et al had already disclosed a method for making fluorescence transgenic fish displaying fluorescence in the muscle of the fish. In addition, Bryan et al had described that novelty

items such as transgenic fish comprising fluorescent genes could be designed for entertainment, recreation and amusement including use of the item to attract attention (col. 8, lines 25-29). One of ordinary skill in the art would have been motivated to modify the method of Higashijima to replace GFP with other variants of fluorescent gene such as EBFP, EYFP, ECFP as disclosed by Yang et al/ CLONTECHniques. This would have allowed person of ordinary skill to express different fluorescent color for distribution of transgenic fish displaying different color or combination of different colors as novelty item for display at public place as suggested by Bryan.

One who would have practiced the invention would have had reasonable expectation of successfully obtaining a transgenic fish comprising fluorescent gene and distributing in the market because Higashijima already taught a method for making fluorescent transgenic fish and Bryan had taught fluorescent transgenic fish could be made for entertainment, recreation and amusement including use of the item to attract attention. One of ordinary skill in art would have been motivated to combine the teaching Higashijima, Yang et al/ CLONTECHniques and Bryan because a fluorescent transgenic fish comprising one or more fluorescent gene operably linked to a promoter would have provided fluorescent fish that would have attracted attention upon distribution of color displaying transgenic fish as a novelty item in a place of normal or ordinary uses of such an item (pet store or ornamental fish market) as taught by Bryan.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

New-Double Patenting

Claims 1-3, 9-16, 19-21, 24, 30-32, 35-42 are rejected on the ground of nonstatutory double patenting over claims 1-7 of U. S. Patent No. 7,135,613 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: In the instant case, even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass a transgenic fish comprising a chimeric gene comprising a promoter that drives the expression of a structural gene in said fish, wherein the transgenic fish contains said promoter in germ cells and/or in somatic cells and which is capable of breeding with either a said transgenic fish or a non-transgenic fish to produce viable and fertile transgenic progeny. It is noted that structural gene is specifically exemplified as different fluorescent gene in US patent 7,135,613. Therefore, instant claims differ only with respect to a broader scope distributing transgenic fish which encompass those specifically claimed in patent 7,135,613.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ellenberg, J., et al. (1998) BioTechniques 25: 838–846 teach variants of GFP with red- and blue-shifted fluorescence emissions that have been characterized, and possibly could be used for double labeling with two different-colored fusion proteins.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
Examiner, AU 1632

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600